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| 09/744,431 | 01/22/2001 | James Arthur Hoffmann | X-12383M | 5086 |

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|---|
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| ART UNIT | PAPER NUMBER |
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| 1647 | 10 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . 09/744,431 | Applicant(s) HOFFMANN ET AL. | |
|---|---|---|---|
| | Examiner Regina M. DeBerry | Art Unit 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *92-140* is/are pending in the application.

4a) Of the above claim(s) *107-109 and 118-140* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-106 and 110-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *92-140* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Status of Application, Am ndm nts and/or Claims***

The information disclosure statement filed 27 July 2001 and 17 August 2001 (Paper No. 5 and 7) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits. The amendment filed 22 January 2001 (Paper No. 6) has been entered in full. Claims 1-91 were cancelled.

Applicant's election with traverse of Group I (claims 92-106, 110-117) in Paper No. 9 is acknowledged. The traversal is on the grounds that there is no patentable difference between the species as claimed in Groups I and IV. This is not found persuasive. The claims in Group IV are drawn to not only different species of FSH but different variants of human FSH protein. PCT Rules provides for examining one product, one method of making and one method of using the product. Different sequences constitute diverse products, since they have diverse sequences and/or coding regions. The claims in Group I are actually drawn to two products FSH and FSH variant. The requirement is still deemed proper and is therefore made FINAL.

Claims 107-109, 118-140 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

### *Sp cification*

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

### *Priority*

A claim to priority under 35 USC 371 must contain a specific reference to such in the first paragraph of the first page of the specification.

### *Claim Objections*

Claim 116 is objected to because of the following informalities: Claim 116 encompasses a non-elected invention and requires amendment to limit to elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 100 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 100 recites the limitation "wherein the buffer agent". There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 92,93,94,95,96,97,98,99,103, 105, 112-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skrabanja *et al.* EP 0853 945 A1 in view of L'Italien *et al.* US Patent No. 6,136,784.

Skrabanja teaches a stable formulation comprising FSH and polycarboxylic acid or a salt thereof and a thoiether compound (page 3, lines 15-18, 35-38 and page 4, lines 11-13). FSH includes all forms including recombinant FSH, FSH analogs (page 3, lines 44-54) and human FSH (page 3, lines 39-40, claim 10). Skrabanja teaches concentrations of FSH which overlap the concentrations in the instant claims (page 5, lines 11-14). Skrabanja teaches methods of treating infertility by administrating a

gonadotropin (page 5, lines 45-49). Skrabanja does not explicitly state that the patient population is human, however, it is assumed that the patient is human because Skrabanja states, "the patient can simply inject each time the quantity needed" (page 5, lines 41-44). Skrabanja teaches methods of preparing the formulation (pages 5-7 and claims 11-12). Skrabanja teaches an article of manufacture comprising a vial or a pen-injector device. The formulation can be in the form of a cartridge for multiple use (page 5, lines 21-45). It is noted that the limitations in the claims regarding the written instructions are not given patentable weight, since written material is a form of intellectual property protectable by copyright, not patents. Skrabanja does not teach a packaging material comprising a label which indicates that the solution may be held over a period of 24 hours. Skrabanja, however, defines "stabilize", by if addition of a stabilizing compound took longer (e.g. 2 weeks instead of 1 week) to degrade at a set temperature (page 3, lines 55-58). Skrabanja also claims the use of a gonadotropin for the manufacture of a directly injectable liquid medicament for the treatment of infertility (claim 15). Since the claims are drawn to the stability of gonadotropins, the manufacture of the product and Skrabanja suggests the recited concentrations and dilutions, it is assumed that the there would be some sort of information regarding doses, stability, etc. Skrabanja does not teach a formulation comprising the preservatives cited in the instant claims.

L'Italien teaches the formulation of amylin peptides in an aqueous system along with sodium chloride for isotonicity (column 18, lines 25-28 and lines 38-41). Water can be considered a physiologically acceptable buffer. L'Italien states that the use of

antimicrobial preservatives m-cresol, benzyl alcohol and phenol are present in the formulation of product design to allow the patient to withdraw multiple doses (column 18, lines 44-50). The abstract states that these formulations maintain stability upon storage under refrigerated or room temperature conditions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Skrabanja regarding concentrations and various forms of follicle stimulating hormone and preparations of pharmaceutical compositions to use the teachings of L'Italien regarding isotonic agents and antimicrobial preservatives. The motivation and expected success is provided by L'Italien who teaches that the pharmaceutical formulations maintain stability.

Claims 100 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skrabanja *et al.* EP 0853 945 A1 in view of L'Italien *et al.* US Patent No. 6,136,784 and further in view of Carey *et al.* US Patent No. 4,746,508. The teachings of Skrabanja and L'Italien are described above. None of the references disclose the use of sodium phosphate. Carey teaches the administration of FSH and the use of sodium phosphate as a physiologically acceptable carrier (column 9, lines 8-14; column 10, lines 13-17 and claims 38, 47 and 64.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Skrabanja and L'Italien cited above and use the teachings of Carey. The motivation and expected success is provided by Carey

who teaches that sodium phosphate is a physiologically acceptable carrier that also offers buffering capacity, which maintains the pH.

Claims 102, 104 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over above, and further in view of Skrabanja *et al.* EP 0853 945 A1, L'Italien *et al.* US Patent No. 6,136,784 and Carey *et al.* US Patent No. 4,746,508 in view of Boime *et al.* US Patent No. 6,238,890. The teachings of Skrabanja, L'Italien and Carey are described above. None of the references teach the formulation comprising FSH variant of the formula α-subunit: (SEQ ID NO:5) β-subunit: (SEQ ID NO:11)

Boime teaches the amino acid sequences of SEQ ID NO:5 and SEQ ID NO:11 (Please see sequence search query Appendix A and B). Boime states that the α and β subunits of the wild-type heterodimers or their variants or their fragments are covalently linked, optionally through a linker moiety (abstract). Boime states that the normally heterodimeric glycoprotein hormones retain their properties when in single-chain form (column 2, lines 31-35). The single-chain forms of the invention may either be glycosylated, partially glycosylated, or nonglycosylated and the α and β chains that occur in the native glycoprotein hormones or variants of them may optionally be linked through a linker moiety (column 2, lines 36-49; Table 1 column 32-column 33). Boime describes single-chain forms of heterodimers or homodimers (column 4, lines 17-30 and 47-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Skrabanja, L'Italien and Carey cited

above to use the teachings of Boime. The motivation and expected success is provided by Boime who teaches single chain forms of heterodimers or homodimers are more stable. Furthermore, the single chain forms are unique starting materials for identifying truncated forms with the activity of the dimers. The linkage between the subunits permits the protein to be engineered without disturbing the overall folding of the protein. Using variants of the β subunit of FSH will also help identify agonists and antagonist of the glycoprotein hormone activity.

Claims 116 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arpaia *et al.* US Patent No. 5,128,453 in view of Clark *et al.* US Patent No. 5,374,620 and Skrabanja *et al.* EP 0853 945 A1.

Arpaia teaches ampoules of lyophilized FSH (column 10, lines 66-68 and column 11, lines 19-25). Clark teaches stabilizers such as phenol, benzyl alcohol and m-cresol (column 13, lines 43-47). Clark states that the stabilizer is included in astable liquid form of the GH (growth hormone) and IGF-I (insulin-like growth hormone) formulation, but not in a lyophilized form of the formulation. In the latter case, the stabilizer is present in the bacteriostatic water for injection used for reconstitution (column 13, lines 48-53). Clark states GH or IGF-I can be stored in ampoules or vials as an aqueous solution or as a lyophilized formulation for reconstitution (column 14, lines 37-45). It is assumed that the stabilizers present in the bacteriostatic water must be stored in a container. Skrabanja teaches an article of manufacture comprising a pen-injector device (page 5, lines 21-45). None of the references teaches a packaging material

comprising a label which instructs a patient to reconstitute the lyophilized FSH in the preservative solution for use of a period of 24 hours or greater. However, as was stated above, the limitations in the claims regarding the written instructions are not given patentable weight, since written material is a form of intellectual property protectable by copyright, not patents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Arpaia regarding lyophilize formulations of FSH, to store the lyophilized FSH and stabilizer in a pen-injector device as taught by Skrabanja and reconstitute the lyophilize formulation with stabilizers as taught by Clark. The motivation and expected success is provided by Clark who teaches that stabilizers preserve the active ingredients in the formulation so that they do not degrade or become inactive over a reasonable period of time.

## ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
June 27, 2002

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER